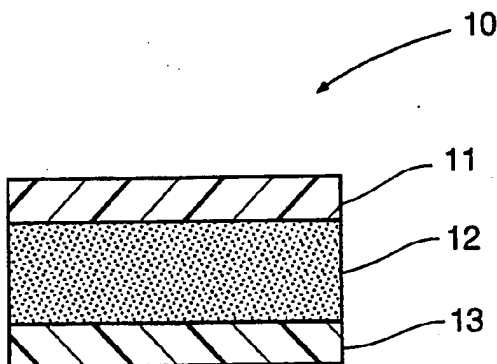




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61F 13/02	A1	(11) International Publication Number: WO 93/14727 (43) International Publication Date: 5 August 1993 (05.08.93)
(21) International Application Number: PCT/US93/00733 (22) International Filing Date: 27 January 1993 (27.01.93) (30) Priority data: 07/827,950 31 January 1992 (31.01.92) US (71) Applicant: CYGNUS THERAPEUTIC SYSTEMS [US/US]; 400 Penobscot Drive, Redwood City, CA 94063 (US). (72) Inventors: ROOS, Eric, J. ; 414 O'Connor Street, Menlo Park, CA 94025 (US). CHIANG, Chia-Ming ; 380 Shad Court, Foster City, CA 94404 (US). FLYNN, Gordon, L. ; 750 Dartmoor, Ann Arbor, MI 48103 (US). SHARMA, Kuldeepak ; 100 N. Whisman, #297, Mountain View, CA 94043 (US).		(74) Agents: CIOTTI, Thomas, E. et al.; Morrison & Foerster, 755 Page Mill Road, Palo Alto, CA 94034-1018 (US). (81) Designated States: AU, CA, FI, JP, KR, NO, NZ, PT, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>

(54) Title: TRANSDERMAL ADMINISTRATION OF BUPRENORPHINE IN THE FORM OF ION PAIR COMPLEXES

**(57) Abstract**

A method and laminated composite for the administration of buprenorphine in the form of an ion complex transdermally to treat pain. The buprenorphine ion pair complex is a buprenorphine cation and an acid anion having the formula $R-M^+$, wherein M^+ is a negatively charged moiety such as carboxy, sulfate, nitrate, nitrite, phosphate and phosphite; and R is linear or branched, substituted or unsubstituted, saturated or mono-, di- or tri-unsaturated alkyl having from about 5 to 20 carbon atoms and substituted or unsubstituted aryl, arylalkyl or phenyl, and is formed by crystallization from a polar/non-polar solvent mixture. The composite (10) comprises an impermeable backing layer (11) and a reservoir layer (12) containing the buprenorphine ion complex and optionally a permeation enhancer combined with a pressure-sensitive adhesive with the amounts of buprenorphine and optional enhancer being sufficient to cause the buprenorphine to pass through the skin at a rate in excess of about $0.05 \mu\text{g}/\text{cm}^2/\text{hr}$. The composite also comprises a release liner lamina (13).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LJ	Liechtenstein	SN	Senegal
CM	Cameroun	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TC	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam
FI	Finland				

-1-

5 TRANSDERMAL ADMINISTRATION OF BUPRENORPHINE
 IN THE FORM OF ION PAIR COMPLEXES

Background of the Invention

Field of the Invention

10 This invention relates to the transdermal
administration of effective dose levels of
buprenorphine to patients. More particularly, it
relates to a transdermal dosage form of buprenorphine
as a buprenorphine ion pair complex and to its use.

15 Prior Art

Buprenorphine is the common name for (5 α ,7 α
(s))-17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-
epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-6,14-
20 ethenomorphinan-7-methanol. This material is sold
under the trademarks Buprenex (Morton-Norwich) and
Tengesic (Reckitt and Coleman). It is described in
United States Patent No. 3,433,791 (1968). It is an
analgesic which demonstrates narcotic agonist-
25 antagonist properties. It has been used principally
for the management of pain associated with surgical
procedures, cancer, accidental trauma, and myocardial
infarction. Buprenorphine is also being used in the
detoxification treatment of heroin addicts due to its
30 narcotic agonist/antagonist properties. Bickel, W.K.,
et al., Chem. Pharmacol. Ther. (1988) 43:1:72-78 and
Fudala, P. J., et al., Clin. Pharmacol. Ther. (1990)
47:4:525-534.

Heretofore, buprenorphine has been
35 administered most commonly by intramuscular injection
or intravenous injection as reported by Norwich Eaton
Pharmaceuticals, Inc., in "Buprenex Prescribing

-2-

Information," Norwich, N.Y., 1986; "Buprenex Compatibility Chart," Norwich, N.Y., 1986; and "Buprenex: Background Data for Review for Pharmacy and Therapeutic Committees," Norwich, N.Y., May 1985.

- 5 See also, Heel, R.C., et al., "Buprenorphine: A Review of Its Pharmacological Properties and Therapeutic Efficacy," Drugs (1979) 17:81-110.

In view of the chronic nature of many of the severe conditions for which buprenorphine is employed, it can often be desired to administer this drug over a prolonged period of time. To that end, the Norwich Eaton publications mention the possibility of slow, prolonged IV administration and Robbie, D.S., has published the results of a trial of sublingual buprenorphine in chronic cancer pain settings in British J. Clin. Pharmacol. (1979) 33:587-90. Additional discussions of sublingual administration of buprenorphine include: Bullingham, R., et al., Clin. Pharmacol. Ther. (1980) 28:667-72; Bullingham, R., et al., Clin. Pharmacol. (1983) 8:332-43; Bullingham, R., et al., British Clin. Pharmacol. (1982) 13:665-73; Rosana, C., et al., Clin. Ther. (1982) 5:61-8; O'Sullivan, G. H., et al., Anaesthesia (1983) 38:977-84; and Adriensen, H., et al, Acta. Anaesthesia Belg. (1985) 36:33-40.

The possibility of transdermal administration of buprenorphine has also been studied. European Patent Application No. 0282156 (Alza Corp., 14 September 1988) teaches that transdermal coadministration of corticosteroids with irritating drugs is advantageous and lists buprenorphine as a drug which might benefit from such coadministration.

United States Patent No. 4,806,341, issued 21 February 1989 to Chien et al. is directed to morphinan narcotic analgesic dosage units in which the analgesic is microdispersed in a solid polymer matrix

-3-

and supplied transdermally. Buprenorphine is listed therein as one of the potentially useful analgesics.

United States Patent No. 4,956,171, issued 11 September 1990 to Chang demonstrated that a
5 transdermal drug delivery system using a "dual permeation enhancer" (sucrose cocoate and methyl laurate) could effectively deliver buprenorphine with a steady state flux of $3.5 \mu\text{g}/\text{cm}^2/\text{hr}$.

United States Patent No. 5,069,909, issued 3
10 December 1991 to Sharma discloses a transdermal drug delivery system for buprenorphine using a permeation enhancer comprising propylene glycol monolaurate in combination with capric acid or oleic acid. Other transdermal drug delivery systems for buprenorphine
15 are disclosed in European Patent Application No. 0432945 (Warner Lambert Company, published 19 June 1991), and European Patent Application No. 0430019.

European Patent Application No. 0368406 (Norwich Eaton Pharmaceuticals, Inc., published 16 May
20 1990) is directed to the transdermal delivery of buprenorphine in a carrier comprising a polar lower alkyl diol or triol solvent and a polar lipid that is a fatty alcohol ester, fatty acid ester, or mixture thereof.

25 PCT Patent Application No. W088/09676 (Warner Lambert, published 15 December 1988) is directed to the use of fatty acids or fatty acid esters as transdermal drug delivery enhancers in aqueous systems and mentions buprenorphine as one of
30 the drugs with which these enhancers might be used. A similar suggestion for non-aqueous systems may be found in United States Patent No. 4,626,539, issued 2 December 1986 to B. Aungst, et al.

T. Ogiso et al., J. Pharm. Sci (1990)
35 79:1065-1071 used fatty acids such as lauric and myristic acids to enhance the percutaneous absorption of propranolol. Ogiso et al. postulated a mechanism by

-4-

which propranolol crossed the stratum corneum as an ion pair complex with the fatty acid, followed by dissociation of the complex and partitioning of propranolol into the epidermal tissue.

5 Most of the proposed systems for transdermal administration of buprenorphine provide a flux that is insufficient for effective treatment of an individual. The use of fatty acid ion complexes with buprenorphine as a method of increasing buprenorphine flux has not
10 been previously suggested.

Statement of the Invention

 It has now been found that one can actually enhance the sustained administration of buprenorphine
15 at therapeutically effective dose levels by delivering it transdermally as a buprenorphine cation complexed with a fatty or aromatic acid anion.

 Thus, in one aspect, this invention provides a buprenorphine ion pair complex comprising a
20 buprenorphine cation and an acid anion having the formula $R-M$, wherein M is a negatively charged moiety such as carboxy, sulfate, sulfite, nitrate, nitrite, phosphate and phosphite; and R is linear or branched, substituted or unsubstituted, saturated or mono-, di-
25 or tri-unsaturated alkyl having from about 5 to 20 carbon atoms and substituted or unsubstituted aryl, arylalkyl or phenyl, and the complex is formed by crystallization from a polar/non-polar solvent mixture.

30 In another aspect of this invention, a method of buprenorphine therapy for an individual is provided by administering a therapeutically effective amount of a buprenorphine ion pair complex comprising a buprenorphine cation and an acid anion having the
35 formula $R-M$, wherein M is a negatively charged moiety such as carboxy, sulfate, sulfite, nitrate, nitrite, phosphate and phosphite; and R is linear or branched,

-5-

substituted or unsubstituted, saturated or mono-, di- or tri-unsaturated alkyl having from about 5 to 20 carbon atoms and substituted or unsubstituted aryl, arylalkyl or phenyl to the individual transdermally.

5 This method can take the form of applying buprenorphine to a predetermined area of the patient's skin adequate to enable the buprenorphine to permeate the area of skin at a rate in excess of about 40 micrograms per hour.

10 In yet another aspect of this invention, a laminated composite for administering the buprenorphine ion pair complex to an individual transdermally through a predetermined area of skin is provided comprising a backing layer that is
15 substantially impermeable to the passage of the buprenorphine ion pair complex; and, a reservoir layer comprising a pressure-sensitive adhesive polymer which contains a buprenorphine ion pair complex.
The basal surface of the reservoir layer is adapted to
20 be adhered to said area of skin. The administration is accomplished by affixing to the patient's skin the composite, which has a contact area with the patient's skin of from 10 to 100 cm² and which makes buprenorphine available to the area of skin for
25 transdermal administration at a rate in excess of 0.05 micrograms per cm² per hour. Preferred administration rates are from about 0.05 to about 5.0 micrograms per cm² per hour.

30 Brief Description of the Drawing

The drawing shows in cross-section an embodiment of a skin patch for transdermal administration of a buprenorphine ion pair complex.

35

-6-

Modes for Carrying Out the InventionDefinitions

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

"Buprenorphine" shall mean (5 α ,7 α (s))-17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-6,14-ethenomorphinan-7-methanol. As used herein, the term encompasses the free base and acid addition salts such as the hydrochloride.

"Penetration enhancement" or "permeation enhancement" as used herein relates to an increase in the permeability of skin to a buprenorphine pharmacologically active agent, i.e., so as to increase the rate at which buprenorphine permeates into and through the skin. A "permeation enhancer" is a material which achieves permeation enhancement of buprenorphine.

"Penetration enhancement" or "permeation enhancement" refers to increased permeability to buprenorphine in the form in which it crosses the skin. This enhancement in the rate of delivery of a drug can result from chemical enhancement or skin enhancement. Chemical enhancement refers to modifications to the drug that increases its partitioning into the skin or stratum corneum, often effected by an enhancing agent. Skin enhancement refers to changes in skin structure that increases the diffusion of a drug across the skin. The mechanism by which the buprenorphine ion pair complex penetrates or permeates the skin is not known with certainty. However, without intending to limit the invention in any way, it is believed that buprenorphine crosses the stratum corneum as an ion pair complex, and at a later time dissociates into uncomplexed buprenorphine.

-7-

"Transdermal" (or "percutaneous") shall mean passage of a material into and through the skin to achieve effective therapeutic blood levels or deep tissue therapeutic levels. Transdermal delivery is to be distinguished from "topical" delivery. By "topical" administration is meant local administration of a topical pharmacologically active agent to the skin as in, for example, the treatment of various skin disorders or the administration of a local anaesthetic. "Topical" delivery intends penetration of a drug into the skin but not through it, i.e., topical administration does not intend actual passage of a drug into the bloodstream.

"Carriers" or "vehicles" as used herein refer to pharmaceutically acceptable carrier materials without pharmacological activity which are suitable for administration with other pharmaceutically active materials, and include any such materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is nontoxic and which does not interact with the drug to be administered in a deleterious manner. Examples of suitable carriers for use herein include non-aqueous materials such as mineral oil, silicone, inorganic gels, glycols and polyols, liquid sugars, waxes, petroleum jelly, and a variety of other oils and polymeric materials.

By a "therapeutically effective" amount of buprenorphine is meant a nontoxic but sufficient amount of uncomplexed buprenorphine to provide the desired therapeutic effect. The desired therapeutic effect is the alleviation of pain or inducement of analgesia in the patient or in the case of heroin or cocaine addicts, the achievement of detoxification.

The present invention involves the transdermal administration of buprenorphine as a low-melting, hydrophobic ion pair complex. A "buprenorphine ion pair complex", as used herein,

-8-

refers to a complex formed by a buprenorphine cation (protonated at the basic nitrogen) and a hydrophobic organic anion. The buprenorphine ion pair complex fully or partially dissociates in aqueous solution.

- 5 However, the complex dissolves in non-aqueous solvents, the ion pair remaining together and undissociated.

Ion pair complexation is also possible for transdermal administration of a broad range of opioids including buprenorphine. The term "opioids" as used herein means any natural or synthetic opioid analgesic, such as morphine, oxymorphone, fentanyl, sufentanil, meperidine, propoxyphene, or oxycodone; any natural or synthetic narcotic antagonist such as nalmeferene, naloxone or naltrexone; any natural or synthetic mixed opioid agonist/antagonist such as nalbuphine, butorphanol, buprenorphine or pentazocine.

The buprenorphine ion pair complex has two components -- a buprenorphine cation and an acid anion. The buprenorphine cation is protonated at the N-17 amine site. The acid anion is generally a fatty acid anion or aromatic acid anion.

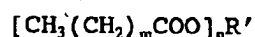
More specifically, the acid anion of the invention is an acid anion having the formula $R-M^-$, wherein M^- is a negatively charged moiety selected from the group consisting of carboxy, sulfate, sulfite, nitrate, nitrite, phosphate and phosphite; and wherein R is selected from the group consisting of linear or branched, substituted or unsubstituted, saturated or mono-, di- or tri-unsaturated alkyl having from about 5 to 20 carbon atoms and substituted or unsubstituted aryl, arylalkyl or phenyl. The substitutions include neutral, positively charged, and negatively charged substitutions. Neutral substitutions include hydroxy, alkoxy, halo (fluoro, chloro, bromo, iodo), nitro, formyl, keto, alkanoyl, amido, and imido groups. Positively charged substitutions include amino, diazo

and guanido groups. Negatively charged groups include carboxy, sulfate, sulfite, nitrate, nitrite, tosylate, brosylate, mesylate, phosphate, phosphite, and selenate groups. In preferred embodiments of this invention, M is carboxy and R is unsubstituted or halo-substituted, branched or linear alkyl.

The buprenorphine ion pair complex is easily formed by crystallizing the cation and anion together from a solvent mixture comprising a non-aqueous polar and a nonpolar solvent. Usually the buprenorphine and acid are added as free buprenorphine base and protonated acid, and the cation and anion are formed in solution. Any solvent mixture that solubilizes the buprenorphine cation and acid anion is acceptable. In such a nonaqueous solvent, the ion pair complex will not ionize. A preferred solvent mixture is ethanol:hexane, more preferably in a 1:5 (v/v) ratio.

The solution from which the buprenorphine ion pair complex is crystallized will contain the buprenorphine cation and acid anion in molar ratios ranging from about 5:1 (cation:anion) to about 1:100. More preferably, the molar ratio is between about 1:1 and 1:3.

After the buprenorphine ion pair complex is crystallized from the solvent mixture, it is at least partially redissolved in a nonaqueous solvent, where the ion pair remains complexed. Preferably, the solvent is a glycol such as propylene glycol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether or Softigen 767, an ester of the formula



wherein m is an integer from 8 to 16, n is 1 or 2 and R' is lower alkyl, ethylene glycol, propylene glycol, or mixtures thereof. Most preferably, the solvent is propylene glycol monolaurate (PGML) or propylene glycol (PG).

-10-

The solubilized buprenorphine ion pair complex is ultimately administered transdermally to a patient. This mode of administration may be carried out by affixing a buprenorphine-containing laminated composite to the patient's skin.

A representative laminated composite for administering buprenorphine transdermally to humans to induce analgesia is shown in the drawing. This composite, generally designated 10, comprises a backing lamina 11, a buprenorphine reservoir lamina 12, and a release liner lamina 13.

The backing layer provides a protective covering for the composite and may itself be a single layer or a multiplicity of layers. For instance if the composite is to be worn for periods in excess of a day or two, it is desirable to make the backing from an elastomeric polymer such as polyurethane, polyether amide, or copolyester. In order to insure the occlusiveness of such elastomeric polymers, it may be necessary to place a layer of an occlusive material, such as polyisobutylene, between the backing and the reservoir. For devices that are intended to be worn for shorter durations, the backing may be made from relatively flexible but not elastomeric occlusive polymers such as polyester, polyethylene, or polypropylene. The thickness of the backing layer will normally be in the range of about 15 microns to about 250 microns.

The reservoir lamina is composed, in its most elementary form, of the buprenorphine ion pair complex in the amount of 1 to 12% by weight (preferably 2 to 10% by weight) and a pressure-sensitive adhesive. The pressure-sensitive adhesive is generally a material such as an isobutylene, a silicone, or an acrylate adhesive. Representative adhesives include: polyisobutylene; silicone adhesives such as silastic, Dow Corning X7-2920 silicone

-11-

adhesive or Dow Corning 2675 silicone adhesive, with or without added silicone-oil tackifier; and non-aqueous solvent-based acrylate materials. Acrylate copolymer materials are available commercially. For example, Monsanto Chemical Company distributes a family of vinyl acetate-acrylate copolymer resin solutions under the trademarks GELVA® 737 and GELVA® 788 and Morton Thiokol, Inc. distributes acrylate copolymers under the trademarks Morstik 207A and Morstik 607.

These acrylate copolymer materials can be used separately or in mixtures. Several specific materials which give good results are the Morstik 607 materials, the GELVA® materials, which are believed to be based on 2-ethylhexyl acrylate, and mixtures of from about 20:1 to about 1:1 GELVA® 737 and GELVA® 788 (ratios given as weight ratios of GELVA® 737 to GELVA® 788). All of these materials are solvent based but form films following casting and removal of the solvent. The term "solid" is used broadly since the "solid" product is generally a tacky, amorphous (i.e. pressure sensitive adhesive) non-flowing material.

These materials are typically available as solutions in organic solvents such as toluene, ethanol, isopropanol, ethyl acetate and the like. These solvents are substantially eliminated from the matrix during fabrication.

These matrix materials have the property of being high tack pressure-sensitive adhesives when dried and/or cured. Thus, the matrices formed from these materials can adhere directly to the patient's skin without the need for additional separate adhesives.

An optional third component of the reservoir lamina is one or more permeation enhancers. The enhancer is present in the layer in amounts ranging up to about 25% by weight. Preferred use levels are from

-12-

2% to 20% and especially 5% to 20% by weight.

Representative enhancers are esters of the formula

$[\text{CH}_3(\text{CH}_2)_m\text{COO}]_n\text{R}'$ in which m is an integer from 8 to 16, preferably 8 to 12, most preferably 10; n is 1 or 2,

5 preferably 1; and R' is a lower alkyl ($\text{C}_1\text{-C}_3$) residue which may be substituted with 0 to 2 hydroxyl groups, or a mixture of such an ester or methyl laurate and diethylene glycol monomethyl or monoethyl ether. The volume ratios of ester to ether in such mixtures will

10 normally be in the range of 90:10 to 50:50. The use of such mixtures as permeation enhancers is described in commonly owned copending U.S. patent application Ser. No. 327312, filed 22 March 1989. The preferred esters of the above formula are lower alkyl ($\text{C}_1\text{-C}_3$)

15 esters of lauric acid, with propylene glycol monolaurate (PGML) being particularly preferred. It will be appreciated by those skilled in the art that commercially available PGML is normally a mixture of propylene glycol monolaurate, propylene glycol
20 dilaurate and either propylene glycol or methyl laurate or both. Thus "propylene glycol monolaurate" is intended to encompass the pure compound as well as the mixture that is sold commercially. It is also intended that the enhancer may be composed of a
25 mixture of said esters, by themselves or in combination, with one or both of the mentioned ethers.

Other enhancers which may be employed to advantage include diethylene glycol monomethyl and monoethyl ethers, lauric acid, lauric alcohol, capric
30 acid, oleic acid, glycerol oleate, and the like. In using some of these materials care must be taken to avoid irritation which may accompany these materials at high use levels.

Particularly preferred enhancers are the
35 vegetable oils, which are fatty acid esters that may also contain some free fatty acid. Vegetable oils of this invention include corn oil, sesame oil, peanut

-13-

oil, coconut oil, soybean oil, almond oil, olive oil and mixtures thereof.

The thickness of the reservoir layer will normally be in the range of 20 microns to 150 microns, preferably 25 microns to 100 microns.

The reservoir lamina plays two functional roles, namely, it is a reservoir for the buprenorphine ion pair complex and the solvent/enhancer, and because of its composition, it is adhesive and its basal surface provides the means by which the composite is affixed to the skin. The basal release liner lamina 13 is a protective coating for the reservoir lamina during storage and prior to affixation to the skin. This layer is removed from the composite before the composite is affixed to the skin.

The reservoir layer may be formulated by conventional methods known in the field of transdermal drug delivery devices and the three layers assembled into a laminated composite by like methods. These methods and specific embodiments of the invention are further illustrated by the following Experimental Results and Examples. These examples are not intended to limit the invention in any manner.

This invention will be further described with reference to the following Experimental Results and Examples. The Experimental Results section provides details of the methodology employed. The Examples describe the production and testing of specific buprenorphine delivery devices.

Experimental Results

Preparation of Buprenorphine Base:

Buprenorphine base was prepared from its HCl salt. A known amount of commercial buprenorphine HCl was dissolved in water, followed by the addition of saturated solution of Na_2HCO_3 , to precipitate buprenorphine base. The precipitate was then filtered

-14-

and washed several times with cold deionized water to remove excess Na_2HCO_3 . The white residue was then dried overnight in air. The dried residue was added to a water:ethanol (80:20) mixture, and heated to 60°C to dissolve the free base, followed by immediate filtration. Upon cooling, the buprenorphine base crystallized. The rhombic shaped crystalline product was then filtered and dried under a gentle stream of nitrogen. The purity of the base was checked by melting point and HPLC assay. The melting point of the base was 210°C, virtually the same as reported in the literature. The purity of the base by HPLC assay was 99%.

Preparation of Buprenorphine Ion Pair

Complex: A buprenorphine ion pair complex was formed by dissolving free buprenorphine base and the appropriate acid (e.g., capric, myristic, lauric) in a mixture of 5:1 hexane ethanol. The solvent was then evaporated and the remaining substance was recovered as the complex.

Skin Preparation: Human cadaver skin was used for permeation studies. Frozen skins were thawed and epidermal layers (stratum corneum + viable epidermis) separated from dermatomed skin by immersion in water at 60°C for 2 minutes. The heat-separated epidermal layer was used for studies or stored at -20°C for later studies.

Skin Permeation Method:

Flow-Through Cells:

The flow-through diffusion cells (LGA) have a 7.5 ml receiver compartment and an inlet and outlet to allow flow of solvent. The receptor fluid (phosphate buffer at pH 6.0) was pumped from a temperature-controlled reservoir into and through the cell by a peristaltic pump, and collected in test tubes situated in an automatic fraction collector.

-15-

The collector allows for simultaneous collection from a number of cells and replacement of test tubes with a fresh set at predetermined intervals. Both the Franz cells and the flow-through cells were made up of glass and were jacketed for temperature control. 250 μ L of suspension of buprenorphine in a vehicle was used as the donor phase.

Static Cells: In some experiments, static, side-by-side diffusion cells were used. Skin sections were mounted carefully between the half-cells of the diffusion cell and fastened with a rigid clamp. The receiver compartment was filled with phosphate buffer of pH 6.0 (isotonic). The donor compartment was charged with a saturated solution of buprenorphine in an appropriate vehicle or enhancer. The diffusion cells were placed in an oven and the temperature of the diffusion cell contents was maintained at 32°C. Stirring was set at 200 rpm throughout the experiment. At predetermined times, either one ml of receiver content was withdrawn and replaced with previously warmed (32°C) fresh receiver fluid or the whole receiver contents were emptied and replaced with fresh receiver fluid. Samples were taken from the donor compartment at the beginning of the experiment to determine the concentration of drug. The samples were assayed by HPLC.

Assay Procedure: Buprenorphine was assayed by HPLC using UV-detection at 210 nm. A μ -Bondapak C₁₈ column with acetonitrile-buffer pH 5.0 (45:55) as a mobile phase was used for chromatographic resolution. Calibration curves were obtained by plotting the peak height or area of the authentic drug as a function of drug concentration. Standard curves demonstrated linearity over the concentration range encountered in samples.

-16-

Data Analysis: Skin flux was determined from the following equation:

$$\frac{dM}{dt} = J = A \times P \times \Delta C$$

where J is the skin flux, P is the permeability coefficient and ΔC is the concentration gradient across the membrane, which is assumed to be the same as donor concentration. The skin flux was determined from the slope of the plot of cumulative amount of buprenorphine permeated (M) versus time (t).

Pharmacokinetics of Buprenorphine: The basic pharmacokinetic parameters for buprenorphine are summarized in Table 1.

TABLE 1: Pharmacokinetics of Buprenorphine¹

Parameter	
Daily dose	1.2 mg/day (i.v., tid)
$T_{1/2\beta}$	3.1 ± 0.6 h
Cl_T	77 ± 5 L/h
V_{dis}	188 ± 35 L
MEC (analgesics)	0.5 to 0.7 ng/ml
K_o (J_{dis})	38 to 54 μ g/h
Desired delivery rate from 20 cm ² patch	1.9 to 2.7 μ g/cm ² /h

¹Roy S. Bullingham et al. Br. J. Clin. Pharmac. 13:665-673 (1982).

Based on these values, the input rate or percutaneous absorption rate (J_{dis}) for transdermal delivery was calculated from Cl_T times C_{ss} . This value and the desired delivery rate as calculated are also presented in Table 1.

-17-

ExampleTransdermal Administration of
Buprenorphine Ion Pair Complex System

The following Tables 2-3 compare the skin
5 flux of uncomplexed buprenorphine with various
buprenorphine ion pair complexes prepared as described
above.

TABLE 2. Permeation of buprenorphine compared as free
10 base, hydrochloride, and various ion pair complexes.

	Formulations	Skin Flux
		$\mu\text{g}/\text{cm}^2/\text{hr}$
	5% Bup Base, 3.7% Capric Acid, 91.3% PG	3.2 ± 2.5
	5% Bup Base, 4.3% Lauric Acid, 90.7% PG	4.8 ± 1.1
15	5% Bup Base, 4.9% Myristic Acid, 90.1% PG	6.7 ± 1.3
	5% Bup Base, 95% PG	0.16 ± 0.07
	5% Bup HCl, 95% PG	0.62 ± 0.37

The percentages of base to fatty acid express a 1:2
20 molar ratio.

TABLE 3. Permeation of buprenorphine free base
compared with complexed and uncomplexed fatty acids.

	Formulations	Skin Flux
		$\mu\text{g}/\text{cm}^2/\text{hr}$
25	5% Bup in 95% PG	0.15 ± 0.05
	5% Bup HCl, 4.5% Myristic Acid in 90.5% PG	3.2 ± 0.75
	5% Bup, 4.9% Myristic Acid (Uncomplexed) in 90.1% PG	1.4 ± 0.14
30	5% Bup, 4.9% Myristic Acid (Complexed) in 90.1% PG	4.9 ± 1.2

The percentages of buprenorphine to fatty acid express
a 1:2 molar ratio.

-18-

Claims

1. A buprenorphine ion pair complex comprising:

- 5 (a) a buprenorphine cation and, associated therewith,
- (b) an acid anion having the formula $R-M^-$, wherein M^- is a negatively charged moiety selected from the group consisting of carboxy, sulfate, sulfite, nitrate, nitrite, phosphate and phosphite, and wherein
- 10 R is selected from the group consisting of linear or branched, substituted or unsubstituted, saturated or mono-, di- or tri-unsaturated alkyl having from about 5 to 20 carbon atoms and substituted or unsubstituted aryl, arylalkyl or phenyl,
- 15 wherein said complex is formed by crystallization from a mixture of polar and non-polar solvents.

2. The buprenorphine ion pair complex of

20 claim 1 wherein said complex is non-ionizable in a non-aqueous solvent and has a melting point below 200°C.

3. The buprenorphine ion pair complex of

25 claim 1 wherein R is linear or branched, unsubstituted or halo-substituted, saturated or mono-, di- or tri-unsaturated alkyl.

4. The buprenorphine ion pair complex of

30 claim 1 wherein M^- is carboxy.

5. The buprenorphine ion pair complex of claim 4 wherein M^- is carboxy.

35 6. The buprenorphine ion pair complex of claim 2 wherein the non-aqueous solvent is selected

-19-

from the group consisting of propylene glycol and propylene glycol monolaurate.

7. The buprenorphine ion pair complex of claim 1 wherein the molar ratio of the buprenorphine cation to the acid anion in said complex is between about 1:1 and 1:3.

8. A method for providing buprenorphine therapy to an individual in need of such therapy comprising administering a therapeutically effective amount of a buprenorphine ion pair complex comprising:

(a) a buprenorphine cation; and, associated therewith,

(b) an acid anion having the formula $R-M^-$, wherein M^- is a negatively charged moiety selected from the group consisting of carboxy, sulfate, sulfite, nitrate, nitrite, phosphate and phosphite, and wherein R is selected from the group consisting of linear or branched, substituted or unsubstituted, saturated or mono-, di- or tri-unsaturated alkyl having from about 5 to 20 carbon atoms and substituted or unsubstituted aryl, arylalkyl or phenyl,

to the individual transdermally through a predetermined area of skin adequate to enable the buprenorphine ion pair complex to permeate the area of skin at a rate in excess of about 20 μg per hour.

9. The method of claim 8 wherein said complex is non-ionizable in a non-aqueous solvent and has a melting point below 200°C.

10. The method of claim 8 wherein R is linear or branched, unsubstituted or halo-substituted, saturated or mono-, di- or tri-unsaturated alkyl.

-20-

11. The method of claim 8 wherein M is carboxy.

12. The method of claim 10 wherein M is carboxy.

13. The method of claim 9 wherein the non-aqueous solvent is selected from the group consisting of propylene glycol and propylene glycol monolaurate.

10

14. The method of claim 9 wherein the individual is a human and the buprenorphine ion pair complex is administered to the individual at a rate of about 20 to about 100 $\mu\text{g/hr}$.

15

15. The method of claim 14 wherein the individual is an individual in pain and the amount of the buprenorphine ion pair complex is adequate to alleviate the pain.

20

16. The method of claim 14 wherein the individual is a narcotic addicted individual and the amount of buprenorphine ion pair complex is adequate to maintain the individual to eventually detoxify the individual's addiction by programmed withdrawal.

25

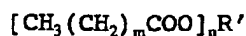
17. The method of claim 14 wherein the buprenorphine ion pair complex is administered concurrently or sequentially in combination with a permeation enhancer.

30

18. The method of claim 17 wherein said permeation enhancer is selected from the group consisting of propylene glycol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, capric acid, oleic acid, Softigen 767, esters of the formula

35

-21-



wherein m is an integer from 8 to 16, n is 1 or 2 and R' is lower alkyl, ethylene glycol or propylene glycol, and mixtures thereof.

5

19. The method of claim 17 wherein the permeation enhancer is a vegetable oil.

20. The method of claim 19 wherein the vegetable oil is selected from the group consisting of corn oil, sesame oil, peanut oil, coconut oil, soybean oil, almond oil, olive oil and mixtures thereof.

21. The method of claim 8 wherein the molar ratio of the buprenorphine cation to the acid anion in the buprenorphine ion pair complex is from about 1:1 to about 1:3.

22. A laminated composite for administering a buprenorphine ion pair complex to an individual transdermally through a predetermined area of skin comprising:

(a) a backing layer that is substantially impermeable to the passage of the buprenorphine ion pair complex; and, adjacent thereto

(b) a reservoir layer comprising a pressure-sensitive adhesive polymer which contains the buprenorphine ion pair complex, said complex comprising:

a buprenorphine cation and, associated therewith,
an acid anion having the formula R-M,
wherein M is a negatively charged moiety selected from the group consisting of carboxy, sulfate, sulfite, nitrate, nitrite, phosphate and phosphite, and wherein R is selected from the group consisting of linear

-22-

or branched, substituted or unsubstituted,
saturated or mono-, di- or tri-unsaturated
alkyl having from about 5 to 20 carbon atoms
and substituted or unsubstituted aryl,
5 arylalkyl or phenyl,

wherein the basal surface of said reservoir layer is
adapted to be adhered to said area of skin and further
wherein the amount of said complex in said reservoir
layer is sufficient to enable a therapeutically
10 effective amount of buprenorphine to be administered
at a rate in excess of about $0.1 \mu\text{g}/\text{cm}^2$ skin/hr to the
individual through said predetermined area of skin
over a sustained time period.

15 23. The laminated composite of claim 22
wherein said buprenorphine ion pair complex is non-
ionizable in a non-aqueous solvent and has a melting
point below 200°C .

20 24. The laminated composite of claim 22
wherein R is linear or branched, unsubstituted or
halo-substituted, saturated or mono-, di- or tri-
unsaturated alkyl.

25 25. The laminated composite of claim 22
wherein M is carboxy.

26. The laminated composite of claim 24
wherein M is carboxy.

30 27. The laminated composite of claim 23
wherein the non-aqueous solvent is selected from the
group consisting of propylene glycol and propylene
glycol monolaurate.

35

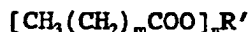
-23-

28. The laminated composite of claim 22 wherein the pressure-sensitive adhesive polymer is a water-base acrylate.

5 29. The laminated composite of claim 22 wherein the reservoir layer additionally comprises a permeation enhancer.

10 30. The laminated composite of claim 29 wherein the permeation enhancer is dissolved in the reservoir layer.

15 31. The laminated composite of claim 30 wherein the permeation enhancer is selected from the group consisting of propylene glycol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, capric acid, oleic acid, Softigen 767, esters of the formula



20 wherein m is an integer from 8 to 16, n is 1 or 2 and R' is lower alkyl, ethylene glycol or propylene glycol, and mixtures thereof.

25 32. The laminated composite of claim 30 wherein the permeation enhancer is a vegetable oil.

30 33. The laminated composite of claim 32 wherein the vegetable oil is selected from the group consisting of corn oil, sesame oil, peanut oil, coconut oil, soybean oil, almond oil, olive oil and mixtures thereof.

35 34. The laminated composite of claim 22 wherein the molar ratio of the buprenorphine cation to the acid anion in the buprenorphine ion pair complex is from about 1:1 to 1:3.

-24-

35. The laminated composite of claim 22 further comprising a peelable release liner adjacent to the reservoir layer.

5 36. A composition for the transdermal administration of a buprenorphine ion pair complex to an individual comprising:

(a) a buprenorphine cation;

10 (b) an acid anion having the formula $R-M^-$, wherein M^- is a negatively charged moiety selected from the group consisting of carboxy, sulfate, sulfite, nitrate, nitrite, phosphate and phosphite, and wherein R is selected from the group consisting of linear or branched, substituted or unsubstituted, saturated or
15 mono-, di- or tri-unsaturated alkyl having from about 5 to 20 carbon atoms and substituted or unsubstituted aryl, arylalkyl or phenyl;

(c) a permeation enhancer; and

(d) a pharmaceutically acceptable carrier.

1/1

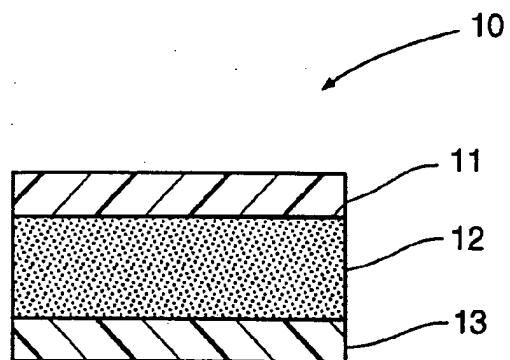


FIG. 1

INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/US93/00733

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61F 13/02

US CL :424/448

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/448; 514/282

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

 APS: Ion(w) Pair; Buprenorphine; Butorphanol; Narcotic and
 (agonist or antagonist); Buprenex or Tengesic; Transdermal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,464,378 (HUSSAIN) 07 AUGUST 1984 See column 1, line 59 through column 2, line 2; column 9, lines 43-50 and column 10, lines 21-22.	1-21 and 36
A	US, A, 4,626,539 (AUNGST ET AL) 02 DECEMBER 1986, See entire document.	1-21 and 36
Y	US, A, 4,806,341 (CHIEN ET AL) 21 FEBRUARY 1989; See column 2, lines 31-45; column 3, lines 33-38; column 11, lines 33-40.	1-36
A	US, A, 4,956,171 (CHANG) 11 SEPTEMBER 1990 See column 3, lines 24-46.	18-20

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be part of particular relevance	X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	A*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

25 MARCH 1993

Date of mailing of the international search report

07 MAY 1993

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
 Box PCT
 Washington, D.C. 20231

Facsimile No. NOT APPLICABLE

Authorized officer

D. GABRIELLE PHELAN

Telephone No. (703) 308-2351

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/00733

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,026,556 (DRUST ET AL) 25 JUNE 1991 See column 4, lines 52-53 and column 6, lines 40-50.	1-36
A	US, A, 5,069,909 (SHARMA ET AL) 03 DECEMBER 1991; See entire document.	1-36